December 4, 1952

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Dear Bernie:

Thank you for your letter of December 2, and your kind remarks on our paper. I agree that the tryptophane.... story needs some further examination. Now that you are so close to Norton, why don't you plan how to settle it more decisively? We chose the best reference we could find at the time; we had the impression from you that more along the same line was in the works, and it was fortunate that the paper coincided with yours.

Concerning drug-resistance in heterozygotes, it is apparent from your letter that the genetic end of it is going to be as tricky as the scoring. Norton has not had a great deal of experience with E. coli heterozygotes, and there is a good deal of complexity about it. Not the least is the choice of stocks: we don't have the ideal combinations of markers, and it will take some thought to make the best compromise, and perhaps some work to develop them. It is likely not to be just a matter of sending you one or two stocks. I would suggest, therefore, a slightly different arrangement: namely, that we set up the heterozygotes with the best combinations we can, and that we send them to you for further testing.

Among the things we don't have are a) a Het Lac$_4$-, and b) a Het with nutritional markers other than M- of T1-. The inheritance of Het is very capricious, and I have not be able to carry through other recombinations. I am not too greatly concerned about this, however. The important comparison is between the diploids and the segregants from them. Unless M is very closely linked to your resistance factors, it should be possible to keep it out of the picture. I would suggest that the first absolute necessity is some preliminary mapping of resistance in crosses of 58-161 x 677 derivs., especiall with a view to finding linkages with sugar markers. If there is linkage to or S, the project may be so difficult that it would be best to defer it ur the segregational behavior of this region is cleared up. If, however, the is linkage to Lac, V_1, Xyl, B_1, or Mtl we should have very little troubl it will be important to know what linkage relationship to use as a guid picking out the best heterozygotes for further study.

I have been assuming that you have some single-step selections likely to be represented by single factors. If you have a pleiotropic situation, there will be no profit in working with the second order of complexity in diploids until after a study of the distribution of the individual factors in haploid crosses has been completed.

I hope that this does not seem unduly discouraging, but there is no point doing a job as delicate as this without doing and planning it correctly. I am ready to do my share on it, if you think the necessary requirements can feasibly be met. I would be very happy to unload the complexities of heterozygote analysis on anyone who was willing to pay the price of a detailed, unhurried genetic analysis. For a more limited objective, there are so many devious bypaths, and traps that we have had to fight through once, that I can foresee nothing but trouble from an unreserved distribution of these stocks. (I think the 1951 CSH paper illustrates adequately what I mean). This is not to say that an absolutely decisive answer cannot be obtained from a reasonable expenditure of effort.

For a more concrete recapitulation then, I suggest that the necessary next step is a preliminary mapping, using prototrophs from 58-161 x 677-der. If the linkage relationships are optimistic, I will then get you heterozygous prototrophs segregating the linkage marker, and presumably the resistance factor, and send them to you. These can then be scored for resistance, and compared with M+ segregants also carrying the linkage markers// alternatives. If the linkage relationships are especially favorable, it may be feasible to develop auxotrophs of other sorts carrying the resistance factors, and cross them with T-L-Het stocks, if necessary to avoid M- altogether. (Unfortunately, our third familiar crossing line is proline-serineless!). I don't know whether it will be easier for you to make auxotrophs in the resistant recombinant prototrophs, or vice versa, but there is no certainty that this will be necessary.

Yours sincerely,

Joshua Lederberg

P.S. I'll get on Neurospora.